REMARKS

Claims 1-18, 27, and 28 are pending in the application. Claims 1, 2, 8, 10, 13-18, 27, and 28 are withdrawn as being drawn to non-elected inventions. Applicants reserve the right to prosecute the non-elected claims in subsequent divisional applications. Claim 12 has been canceled. Claims 3-7, 9, and 11 are currently being examined on the merits.

Claim 3 and Claim 9 have been amended to further clarify the intended subject matter of the claimed invention. No new matter has been added by these amendments. Entry of these amendments is respectfully requested.

Withdrawal of previous rejections

Applicants would like to thank the Examiner for withdrawing previous rejections stated in the last office action. Applicants believe that with the amendments offered in this response and the remarks made herein, the remaining rejections should also be withdrawn.

Enablement rejections under 35 U.S.C. § 112, first paragraph:

Claims 3-7 and 9 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The rejection of the claims is improper as the specification does adequately describe the invention so that it may be made and/or used by one of skill in the art.

The Examiner asserts that "the claims recite 'biologically active' and in view of the indefiniteness of this phrase it is not clear if the biologically active fragments are enzymatically active or some other activity" (Office Action, p. 4). Claims 3 and 9, as amended herein, recite "a biologically active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said biologically active fragment has serine hydratase activity," in order to further clarify the meaning of the term "biologically active." The specification states, "(t)he invention is based on the discovery of a new serine dehydratase homolog (SDHH)" and "(t)he invention encompasses a polynucleotide sequence comprising the sequence of SEQ ID NO:2, which encodes SDHH" (specification, p. 15, lines 2-3 and 30-31). Further, a number of methods for expressing a "biologically active SDHH" are discussed

beginning on page 15, line 17 of the specification. In addition, a method for measuring serine dehydratase activity is described (specification, p. 50, lines 4-19). Thus, one of skill in the art would understand that the biological activity referred to in the claims is serine dehydratase activity, and would understand how to make and use fragments with this activity.

Applicants also respectfully note that the only claim that recites a "polynucleotide of 60 nucleotides that encodes a fragment of SEQ ID NO:1" (Office Action, p. 4) is claim 12, which is not mentioned in this rejection, and in any event has been canceled herein. The recited polynucleotides encoding biologically active fragments can be longer than 60 nucleotides, and thus the Examiner's assertion that 60 nucleotide fragments may be too short to encode active polypeptides is not relevant.

With respect to the claimed variants, the Examiner asserts that "the claims encompass variants that are 90% identical that do not have any function ... and as such one would not know how to use such polynucleotides" (Office Action, p. 4). Applicants respectfully reiterate that the claims are directed to polynucleotides, not polypeptides, and thus it is the functionality of the claimed polynucleotides, not the polypeptides encoded by them, that is relevant. Members of the claimed genus of variants may be useful even if they encode proteins that lack serine dehydratase activity.

For example, the variant polynucleotides could be used for the detection of sequences related to SDHH (see the specification at p. 35, lines 22-26) including SDHH variants that may be associated with disease states, such as the diseases listed in the specification at p. 36, lines 4-13). See the specification at, for example, pp. 36-37 for disclosure of how to use the claimed sequences in diagnostic assays. The variant polynucleotides could also be used in microarrays to identify genetic variants, mutations, and polymorphisms, and for disease diagnosis and development and testing of therapeutic agents (see the specification at, for example, p. 38, lines 1-6). Thus one of ordinary skill in the art would know how to used the claimed variants without any undue experimentation.

The Examiner asserts that, "with regard to immunogenic fragments, the claims encompass any fragment even those that are a single amino acid and as such would not be used for detection of the specific protein of SEQ ID NO:1 and therefore one would not know how to use the invention (Office Action, p. 4)" Claims 3 and 9, as amended herein, recite "an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said immunogenic fragment generates an

antibody that specifically binds to SEQ ID NO:1." This amendment merely restates information that appears in at least two places in the specification for the purpose of further clarifying these claims.

For example, the specification states that "the oligopeptides, peptides, or fragments thereof used to induce antibodies to SDHH have an amino acid sequence of at least about 5 amino acids, and, more preferably, of at least about 10 amino acids" (specification, p. 27, lines 22-24). Immunogenic fragments are further described as "(t)ypically, oligopeptides 15 residues in length" (specification, p. 51, line 31). The specification further recites software (LASERGENE, DNASTAR Inc.) which can be used to determine "regions of high immunogenicity" (specification p. 51, line 27) and suggests that "appropriate epitopes, such as those near the C-terminus or in hydrophilic regions" (specification, p. 51, lines 29-30). In addition, the specification describes methods of preparing monoclonal antibodies to SDHH (specification, p. 27, line 29 through p. 28, line 2). Furthermore, the specificity of any resulting antibody may be tested using the methods described on page 28 (lines 24-30) of the specification or in Example XII (Specification, p. 52, lines 3-5). Thus, there is adequate disclosure to enable one of skill in the art to determine and use an appropriate immunogenic fragment of SEQ ID NO:1 to generate an antibody which binds specifically to SEQ ID NO:1.

Claims 3 and 9, as amended herein, recite "an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said immunogenic fragment generates an antibody that specifically binds to SEQ ID NO:1." The specification describes fragments used to generate these antibodies, and makes clear that one property of these immunogenic fragments is a minimum length greater than one amino acid. Therefore one of skill in the art would understand that single amino acid fragments are not encompassed by the claims as they do not generate specific antibodies.

For at least the above reasons, withdrawal of the enablement rejections under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph:

Claims 3, 6, 7, and 9 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for reciting "biologically active" in claims 3 and 9 because the exact meaning of the phrase is allegedly not clear (Office Action, p. 5).

Claims 3 and 9, as amended herein, recite "a biologically active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said biologically active fragment has serine hydratase activity" in order to further clarify the meaning of the term "biologically active." This amendment is fully supported by the disclosure in the present application (as discussed in greater detail in the previous section), and is put forth merely to further clarify the claims. One of skill in the art would clearly understand that the "biological activity" to which the claims as amended refer is serine dehydratase activity. Therefore, we respectfully request that the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

Written Description rejections under 35 U.S.C. § 112, first paragraph:

Claims 3, 6-7, 9, and 11-12 are rejected under 35 U.S.C. § 112, first paragraph for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claim 12 has been canceled so the rejection as it pertains to claim 12 is moot.

The Examiner asserts that "this disclosure only discloses motifs that are common to SDH and it is not clear which regions are required for enzymatic activity." The disclosure of these motifs provides one of skill in the art guidance to selecting biologically active fragments of SDHH. One of skill in the art need only make plasmid constructs of the polynucleotide fragments of interest and test the encoded polypeptides for serine dehydratase activity using the methods described in Example X (specification, p. 50, lines 4-19). This represents the approach that one of skill in the art would take when studying a polypeptide sequence and thus, does not require undue experimentation. Given that one of ordinary skill in the art has been provided with ample guidance towards selecting polynucleotides encoding biologically active fragments of SEQ ID NO:1, it is not necessary to list all possible such fragments, and such a list would needlessly clutter the specification.

The Examiner states that "(t)he claims also encompass naturally occurring amino acids that are 90% identical to SEQ ID NO:1, however the specification only discloses SEQ ID NO:1" and that "the skilled artisan cannot envision the detailed structure of the encompassed polypeptides".

To address this issue, one must first set forth the proper legal standard. The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Revised Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published December 21, 1999 (Interim Guidelines), which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention[39], i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics[40]. What is conventional or well known to one skilled in the art need not be disclosed in detail[41]. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met[42].

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The Specification provides an adequate written description of the claimed "variants" of SEQ ID NO:2.

SEQ ID NO:2 is specifically disclosed in the application (specification, p. 15, lines 29-31). The Specification further describes variant sequences of SEQ ID NO:2 that have at least about 90% identity to SEQ ID NO:2 (specification, e.g., p. 15, line 33 through p.16, line 7). In addition, SEQ ID NO:1 (the amino acid sequence of SDHH) is specifically disclosed in the application (specification, p. 15, lines 11-24). The specification further describes variants at least 90% identical to SEQ ID NO:1. Given

SEQ ID NO:1 and SEQ ID NO:2, one skilled in the art would recognize naturally-occurring variants of SEQ ID NO:1 or SEQ ID NO:2 having 90% sequence identity to SEQ ID NO:1 or SEQ ID NO:2.

Note that independent claims 3 and 9 recite polynucleotides encoding a polypeptide which, not only has at least 90% sequence identity to SEQ ID NO:1, but also has "a naturally occurring amino acid sequence." Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Given the information provided by SEQ ID NO:1 (the amino acid sequence of SDHH) and SEQ ID NO:2 (the polynucleotide sequence encoding SDHH), one of skill in the art would be able to routinely obtain polynucleotides encoding "a naturally occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1" or a polynucleotide with 90% identity to SEQ ID NO:2. For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. For example:

> As used herein, the term "stringent conditions" refers to conditions which permit hybridization between polynucleotides and the claimed polynucleotides. Stringent conditions can be defined by salt concentration, the concentration of organic solvent (e.g., formamide), temperature, and other conditions well known in the art. In particular, stringency can be increased by reducing the concentration of salt, increasing the concentration of formamide, or raising the hybridization temperature. (Specification, p. 13, lines 3-8)
>
> For example, stringent salt concentration will ordinarily be less than about 750 mM NaCl and 75 mM trisodium citrate, preferably less than about 500 mM NaCl and 50 mM trisodium citrate, and most preferably less than about 250 mM NaCl and 25 mM trisodium citrate. Low stringency hybridization can be obtained in the absence of organic solvent, e.g., formamide, while high stringency hybridization can be obtained in the presence of at least about 35% formamide, and most preferably at least about 50% formamide. Stringent temperature conditions will ordinarily include temperatures of at least about 30°C, more preferably of at least about 37°C, and most preferably of at least about 42°C. Varying additional parameters, such as hybridization time, the concentration of detergent, e.g., sodium dodecyl sulfate (SDS), and the inclusion or exclusion of carrier DNA, are well known to those skilled in the art. Various levels of stringency are accomplished by combining these various conditions as needed. In a preferred embodiment, hybridization will occur at 30°C in 750 mM NaCl, 75 mM

> trisodium citrate, and 1% SDS. In a more preferred embodiment, hybridization will occur at 37°C in 500 mM NaCl, 50 mM trisodium citrate, 1% SDS, 35% formamide, and 100 μg/ml denatured salmon sperm DNA (ssDNA). In a most preferred embodiment, hybridization will occur at 42°C in 250 mM NaCl, 25 mM trisodium citrate, 1% SDS, 50 % formamide, and 200 μg/ml ssDNA. Useful variations on these conditions will be readily apparent to those skilled in the art. (Specification, p. 13, lines 9-26)
>
> In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding SDHH or closely related molecules may be used to identify nucleic acid sequences which encode SDHH. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification (maximal, high, intermediate, or low), will determine whether the probe identifies only naturally occurring sequences encoding SDHH, allelic variants, or related sequences. (Specification, p. 35, lines 14-21)
>
> Probes may also be used for the detection of related sequences, and should preferably have at least 50% sequence identity to any of the SDHH encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:2 or from genomic sequences including promoters, enhancers, and introns of the SDHH gene. (Specification, p. 35, lines 22-26)
>
> See also Example VI at page 47.

Thus, one of skill in the art need not make and test vast numbers of polynucleotides that are based on the polynucleotide sequence of SEQ ID NO:2. Instead, one of skill in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides that already exist in nature. By adjusting the nature of the probe or nucleic acid (*i.e.*, non-conserved, conserved, or highly conserved) and the conditions of hybridization (maximum, high, intermediate or low stringency), one can obtain the claimed variant polynucleotides of SEQ ID NO:2 or polynucleotides which encode variants of SEQ ID NO:1.

Applicants also wish to reiterate that the claims are directed against <u>polynucleotides,</u> not polypeptides; thus the functionality of the encoded polypeptides is not the sole determinant of the claimed genus. Members of the claimed genus may include, for example, mutant alleles associated with diseases, or single nucleotide polymorphisms (SNPs). Such alleles are well known in the art, and have

well known uses as indicators of disease susceptibilities or differential drug responses. It is not necessary to describe specific examples of the members of this genus, since one of skill in the art would reasonably understand what is encompassed by the claims.

Given the sequences of SEQ ID NO:1 and SEQ ID NO:2, one of ordinary skill in the art could readily identify a naturally-occurring polynucleotide sequence having at least 90% sequence identity to the sequence of SEQ ID NO:2, or a polynucleotide encoding a naturally occurring polypeptide having at least 90% identity to SEQ ID NO:1 using well known methods of sequence analysis, without any undue experimentation. There are numerous uses for the claimed invention, any one of which would be available to one of skill in the art given the disclosure of SEQ ID NO:1 and SEQ ID NO:2 in the instant application. These uses include, but are not limited to, expression profiling, toxicological screening, disease detection and diagnosis, and drug discovery (specification, pp. 36-37, pp. 37-38, and p. 39, lines 10-27). These uses are described throughout the specification of the instant application. The Examiner does not dispute that the specification is enabling for the use of the polynucleotide of SEQ ID NO:2. One of skill in the art would know how to use naturally occurring polynucleotide variants with at least 90% sequence identity to the sequence of SEQ ID NO:2, or polynucleotides encoding a naturally occurring polypeptide having at least 90% identity to SEQ ID NO:1, in a comparable manner, for example in expression profiling, toxicological screening, disease detection and diagnosis, and drug discovery.

Accordingly, the Specification provides an adequate written description of the recited polynucleotides.

B. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue

in the present application define polynucleotides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent claim number 11 recites chemical structure to define the claimed genus:

> 11. An isolated polynucleotide selected from the group consisting of...a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:2,

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of the polynucleotide sequence of SEQ ID NO:2 or the amino acid sequence of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the polypeptides encoded by the polynucleotides recited by the claims. Where such functional recitations are included, it adds to the structural characterization of the polypeptides encoded by the recited polynucleotides. The polynucleotides in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

C. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the previously submitted reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <40% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in

this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to polynucleotides encoding serine dehydratases related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as serine dehydratases and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The "variant language" of the present claims recites, for example, a polynucleotide encoding a polypeptide comprising "a naturally-occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 329 amino acid residues). This variation is far less than that of all potential serine hydratases related to SEQ ID NO:1, i.e., those serine dehydratases having as little as 30% identity over at least 150 residues to SEQ ID NO:1.

D. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structures of SEQ ID NO:1 and SEQ ID NO:2. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides defined by the present claims is adequately described, as evidenced by Brenner et al.

For at least the above reasons, withdrawal of the written description rejections under 35 U.S.C. §112, first paragraph, is respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 855-0555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,
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Date: March 13, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim **12** has been canceled.

Claims **3** and **9** have been amended as follows:

3. (Twice Amended.) An isolated polynucleotide encoding a polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1,

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid of SEQ ID NO:1,

c) a biologically active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said biologically active fragment has serine hydratase activity, and

d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said immunogenic fragment generates an antibody that specifically binds to SEQ ID NO:1.

9. (Twice Amended.) A method of producing a polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1,

b) a polypeptide comprising a naturally occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:1,

c) a biologically active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said biologically active fragment has serine hydratase activity, and

d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said immunogenic fragment generates an antibody that specifically binds to SEQ ID NO:1, the method comprising:

i) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding said polypeptide, and

ii) recovering the polypeptide so expressed.